REMARKS

The present invention relates to novel nucleic acid reference standards and methods and kits relating thereto.

Claims 1, 3-10, 12-24 and 26-32 are pending in the present application, with claims 12-22 being withdrawn from consideration as being drawn to non-elected inventions. Claims 2, 11, and 25 were canceled previously without prejudice. Accordingly, claims 1, 3-10, 23, 24, 26-32 are presently under consideration.

Claim 1 has been amended herein, and support for the amendment to claim 1 is found throughout the specification as filed as more fully set forth below. In addition, claims 3-6 and 26-29 have been amended herein. Specifically, claims 3-6 have been amended merely to depend from claim 1. Claims 26-29 have also been amended merely to depend from claim 24 since they depended previously from canceled claim 25. Therefore, no new matter has been added by way of these amendments.

Objections to claims 26-29

The Examiner has objected to claims 26-29 as being dependent from previously canceled claim 25. Applicants have amended claims 26-29 to depend from claim 24, thereby rendering this objection moot.

Rejection of claims 1 and 8-10, pursuant to 35 U.S.C. § 102(b)

Claims 1 and 8-10 stand rejected under 35 U.S.C. §102(b), as being anticipated by Hayatsu et al. (1997, Chem. Pharm. Bull. 45:1363-1368). The Examiner reasons that Hayatsu teaches genomic DNA (calf thymus and salmon testis) bound to chitosan thereby anticipating the reference nucleic acid standard of claim 1, and claims depending therefrom. Applicants respectfully submit that Hayatsu does not anticipate the present invention for the following reasons.

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913,

1920 (Fed. Cir. 1989) (emphasis added). Therefore, Hayatsu must describe each and every element of claims 1 and 8-10, in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not.

Applicants respectfully point out that Hayatsu, teaches binding nucleic acid to particles and then using the nucleic acid thus bound in further processes and assays. Hayatsu emphasizes that the nucleic acids bound to chitosan are "accessible to reagents and enzymes" (Hayatsu at page 1363, left column, first full paragraph). Further, at pages 1366 to 1367, Hayatsu describes how the nucleic acid, while complexed with chitosan, is readily accessible to various substances and enzymes making the DNA-chitosan complex useful for a variety of purposes. *Id.* at page 1367. Therefore, the nucleic acid-chitosan complexes of Hayatsu cannot possibly anticipate the nucleic acid reference standard of claim 1, and claims depending therefrom, in that the target nucleic acid portion of Applicants' reference standard cannot be substantially detected in a nucleic acid assay. This element of the claims is not taught by Hayatsu which emphasizes that the DNA portion of the complex is readily accessible to detection and other manipulations.

Moreover, even assuming Hayatsu teaches calf thymus DNA and salmon testis DNA bound to chitosan, these are complex mixtures of nucleic acids, whereas the claims, as amended, recite that the isolated nucleic acid is a "nucleic acid reference standard" as the term is defined in the specification, at page 26, line 22, to page 27, line 2, and exemplified throughout the specification. Applicants respectfully submit that Hayatsu is not a "nucleic acid reference standard" as recited in the claims because a complex mixture, where the sequence of the nucleic acid is not known cannot possibly anticipate a standard of the present invention where the sequence of the nucleic acid bound with a binding-agent is known. Also, the nucleic acid of the present invention, which is bound with the binding-agent, is not a complex mixture of nucleic acid molecules having a vast number of various nucleotide sequences like those disclosed in Hayatsu. Rather, the standard of Applicants' invention comprises a nucleic acid having a single known sequence bound with the binding agent. Therefore, the complex mixture of uncharacterized nucleic acids of Hayatsu, *i.e.*, calf thymus DNA or salmon testis DNA, which are used as "carrier" nucleic acids according to techniques well known in the art, cannot anticipate the present invention.

Further, claim 1 has been amended herein to indicate that the present invention can be used for validation, standardization, quality control and quality assurance purposes. Support for the use of the reference standard for validation, standardization, quality control and quality assurance purposes is found in lines 9-12 of page 33 in the as-filed specification. Applicants respectfully point out that Hayatsu discloses that the DNA attached to chitosan can be further processed by using a mixture of Dnase I and phosphodiesterase, and thereby demonstrating that the polynucleotides in the chitosan complex are accessible to enzymes and reagents. Nowhere does Hayatsu teach a reference standard nor the use of a reference standard for validation, standardization, quality control and quality assurance purposes.

When claim 1 is read in its entirety, encompassing the limitation that the target nucleic acid is not substantially detected when it is bound with the binding agent and the use of the reference standard for validation, standardization, quality control and quality assurance purposes, as it must be when the claim is read in light of the specification as required by current patent law, Hayatsu does not anticipate the present invention and the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Rejection of claims 1 and 8-10, pursuant to 35 U.S.C. § 102(b)

Claims 1 and 8-10 stand rejected under 35 U.S.C. §102(b), as being anticipated by Kariko et al. (1998, Biochim. Biophys. Acta 1369:320-334). The Examiner is of the opinion that Kariko teaches plasmid DNA (and RNA) bound to a cationic liposome and thereby anticipating the present invention. Applicants respectfully submit that Kariko does not anticipate the present invention for the following reasons.

As discussed elsewhere herein, Kariko must describe each and every element of claims 1 and 8-10, in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not. Applicants respectfully submit that Kariko cannot anticipate Applicants' invention since it does not teach a reference standard at all nor the use of the reference standard for validation, standardization, quality control and quality assurance purposes. Rather, Kariko merely teaches nucleic acid (DNA and RNA)-cationic lipid complexes and cationic lipid-mediated gene transfer to enhance transfection efficiency for both DNA and mRNA in a mammalian cell. Moreover, does not address whether the nucleic acid, when bound with the liposome, is not substantially detected in a nucleic acid assay. Therefore, Applicants respectfully

contend that Kariko does not anticipate the present invention as recited in the amended claims herein, and as discussed elsewhere herein, the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Rejection of claims 1, 3, 5 and 7-10, pursuant to 35 U.S.C. § 102(b)

Claims 1, 3, 5, and 7-10 stand rejected under 35 U.S.C. §102(b), as being anticipated by Boom et al. (EP 0819696 A2). The Examiner is of the opinion that Boom teaches DNA bound to silicon dioxide particles, a nylon filter, diatomaceous earth, particles with 70% ethanol. In addition, the Examiner asserts that Boom teaches RNA, linear and non-linear DNA, and using the DNA in a PCR assay. Applicants respectfully submit that Boom does not anticipate the present invention for the following reasons.

As discussed elsewhere herein, Boom must describe each and every element of claims 1, 3, 5 and 7-10, in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not. Applicants respectfully submit that Boom cannot anticipate Applicants' invention since it does not teach a reference standard at all nor the use of the reference standard for validation, standardization, quality control and quality assurance purposes. Applicants point out that Boom apparently teaches a method of isolating nucleic acid from a starting material such as whole blood, blood serum, urine, feces, cell cultures and the like. Boom further teaches the use of a nucleic acid binding solid phase, i.e., silica particles to isolate and obtain a pure sample of the nucleic acid from an impure starting material. Once again, as discussed regarding Hayatsu's total genomic DNA from either calf thymus or salmon testis, Boom cannot anticipate the invention where the target DNA is not a single purified nucleic acid containing a known sequence as required by the claims, and therefore Boom cannot anticipate the present invention.

Boom emphasizes the isolation of nucleic acid from a sample rather than using a reference standard for validation, standardization, quality control and quality assurance purposes. Therefore, Applicants respectfully submit that Boom cannot anticipate Applicants' invention since it does not teach a reference standard at all nor the use of the reference standard for validation, standardization, quality control and quality assurance purposes.

When claim 1 is read in its entirety, encompassing the limitation that the target nucleic acid is not substantially detected when it is bound with the binding agent and wherein said reference standard is used for validation, standardization, quality control and quality

assurance purposes, as it must be when the claim is read in light of the specification as required by current patent law, Boom does not anticipate the present invention and the rejection under 35 U.S.C. §102(b) should be reconsidered and withdrawn.

Rejection of claim 4, pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claim 4 under 35 U.S.C. §103(a) as being *prima facie* obvious over Boom et al. and Holmberg (EP 0514513 B1). Specifically, the Examiner is of the opinion that Boom teaches DNA bound to polystyrene particles and that Holmberg teaches binding of oligonucleotides to polystyrene solid support derivatized with an amino group. Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the teachings of Boom et al. and Holmberg et al. to arrive at the present invention as recited in claim 4. Applicants respectfully submit that Boom et al. and Holmberg et al. cannot render claim 4 *prima facie* obvious under 35 U.S.C. §103(a). This is because Holmberg, which merely teaches the binding of oligonucleotides to polystyrene solid support derivatized with an amino group, cannot correct the deficiencies of Boom. More specifically, the MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these requirements has been satisfied in the instant matter where Boom, combined with Holmberg, does not teach or suggest all the claim limitations. Also, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

As discussed elsewhere herein, Boom does not teach or suggest a reference nucleic acid standard where the target nucleic acid is not substantially detectable when it is bound with a binding agent, wherein said reference standard is used for validation, standardization, quality control and quality assurance purposes, and where the nucleic acid of Boom is merely a complex mix of unknown complexity and not a "target nucleic acid" as defined and exemplified in the specification as file and recited in the claims. Boom merely teaches a method of isolating nucleic acid from an uncharacterized complex mixture comprising,

among other things, nucleic acids of, at least in part, unknown sequence. Nowhere does Boom teach Applicants' target nucleic acid, which is a well-characterized a reference standard where the sequence of the nucleic acid is known and which does not comprise of a complex mixture, and/or a mixture containing a nucleic acid the sequence of which is either not known or not known in its entirety. Holmberg, which arguably teaches a method of attaching a first nucleoside to the solid support which enables oligonucleotides to be more easily synthesized and purified, wherein said solid support is a polystyrene solid support derivatized with an amino group, does not overcome the deficiency of Boom because Holmberg also does not teach or suggest a target nucleic acid being attached to the support *ab initio*. Instead, Holmberg appears to teach synthesizing a nucleic acid and does not teach binding a full-length nucleic acid of a known sequence to the support. Thus, the teachings of Holmberg do not correct the deficiencies of Boom, which does not teach a target nucleic acid such as is recited by the claims at issue herein, such that the combination of these references does not teach the reference standard of Applicants' invention as recited in the claim 4 as amended. Therefore, the combination of Boom and Holmberg cannot render claim 4 *prima facie* obvious under 35 U.S.C. §103(a), and the rejection should be reconsidered and withdrawn.

Because the combination of Boom and Holmberg does not teach the nucleic acid reference standard of Applicants' invention, there could have been no reasonable expectation that combining these references would produce Applicants' standard, and thus, there would have been no motivation to combine the references to arrive at the present invention. For these additional reasons, the combination of the references cannot render claim 4 *prima facie* obvious under 35 U.S.C. §103(a), and this rejection should be reconsidered and withdrawn.

Rejection of claim 6, pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claim 6 under 35 U.S.C. §103(a) as being *prima facie* obvious over Boom, *supra*, and Matsui et al. (2001, Chemistry Eur. J. 7:1555-1560). As discussed elsewhere herein, the Examiner is of the opinion that Boom teaches DNA bound to silicon dioxide particles, a nylon filter, diatomaceous earth, particles with 70% ethanol. The Examiner also asserts that Matsui et al. teaches the binding of DNA to low alumina zeolites. Therefore, the Examiner reasons that it would have been *prima facie* obvious to combine the teachings of Boom et al. and Matsui et al. to arrive at the present invention as recited in claim 6.

Applicants respectfully submit that Boom et al. and Matsui et al. cannot render claim 6 *prima facie* obvious under 35 U.S.C. §103(a) for the following reasons.

As discussed elsewhere herein, Boom merely teaches a method of isolating nucleic acid from a complex nucleic acid-containing starting material which is not a "target nucleic acid" as defined and exemplified in the specification as filed. Nowhere does Boom teach Applicants' reference standard nor teach using a reference standard for validation, standardization, quality control and quality assurance purposes. More importantly, as discussed previously elsewhere herein, Boom does not teach a target nucleic acid which encompasses a nucleic acid the entire sequence of which is known and where the nucleic acid is homogeneous in that each molecule bound with the binding-agent comprises the same nucleotide sequence. The is simply no the case in Bloom where a complex mixture, comprising nucleic acids of unknown sequence, is applied to a support.

Matsui apparently discloses parameters that influence the adsorption (binding) of proteins and nucleic to synthesized zeolites. Nowhere in Matsui et al. is there teachings of Applicants' reference standard. And Matsui, which does not teach or suggest the "target reference nucleic acid" of the invention, does not correct the deficiencies of Boom such that the combination of these references do not teach the reference standard of Applicants' invention as recited in the claims. Specifically, Matsui does not teach the nucleic acid reference standard of Applicants' invention, a target nucleic acid, and the use of the reference standard for validation, standardization, quality control and quality assurance purposes. Therefore, there could have been no reasonable expectation that combining these references would produce Applicants' standard, and thus, there would have been no motivation to combine the references to arrive at the present invention. For these additional reasons, the combination of the references cannot render the claim 6 *prima facie* obvious under 35 U.S.C. §103(a), and this rejection should be reconsidered and withdrawn.

Rejection of claim 23, 24, 26, 28 and 30-32, pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claims 23, 24, 26, 28 and 30-32 under 35 U.S.C. §103(a) as being rendered *prima facie* obvious over Boom et al. in view of the Stratagene catalog. As discussed elsewhere herein, the Examiner is of the opinion that Boom teaches DNA bound to silicon dioxide particles, a nylon filter, diatomaceous earth, particles with 70% ethanol

and the Stratagene catalog teaches kits, thereby rendering obvious kits comprising the reference nucleic acid of Applicants' invention. Applicants respectfully submit that Boom et al. in view of the Stratagene catalog does not render the invention *prima facie* obvious for the following reasons.

Preliminarily, the Stratagene catalog merely teaches that availability of various kits, and does not correct the deficiencies of Boom et al. That is, Boom, combined with the Stratagene catalog, does not teach or suggest the subject matter of the claims following entry of the present invention. Specifically, as discussed elsewhere herein, Boom does not teach a "target reference standard" as required by the claims, and the nucleic acids of Boom are not used for validation, standardization, quality control and quality assurance purposes. Boom merely teaches the isolation of a nucleic acid from a sample nucleic acid-containing source and has nothing whatsoever to do with a homogeneous sample of nucleic acid, the complete nucleotide sequence of which is known, being bound with a binding-agent. Thus, the combination of Boom and the Stratagene catalog does not teach or suggest all the claim limitations and cannot render the claims *prima facie* obvious.

Additionally, Applicants respectfully submit that the instructional material included with the kit is not "nonfunctional descriptive material" as urged by the Examiner. The instructional material is an integral part of the kit, and recites the methods of the invention. The Stratagene kit does not render the present kit obvious because there is no teaching or suggestion in the Stratagene kit as to the instructional material contained in Applicants' kit. Moreover, the kits cited by the Examiner may comprise a solid support, or binding-agent, that perhaps could be used to arrive at Applicants' kit, but only if one skilled in the art was also armed with the teachings contained in the instructional material of Applicants' kits. Further, the kit of the invention is not obvious by simply combining a kit comprising, for instance, chitosan, because Applicants' kits recite that the kit comprises a nucleic acid standard. That is, a target nucleic acid is already bound with the binding-agent and it is thus provided in the kit as a reference standard. None of the kits suggested by the Examiner, that is, combinations of a Stratagene kit with the above-discussed references of Boom, Matsui, Hayatsu, Holmberg, and Kariko, cannot render the kits of the invention obvious because all the nucleic acids of the references cited by the Examiner, aside from not being a "target nucleic acid" as defined and used by Applicants, become bound with the binding-agent and are not packaged in the kit already bound with the

binding-agent as is required by Applicants' kits. Therefore, even assuming, *arguendo*, Stratagene sold a kit comprising chitosan, the kit does not comprise chitosan already bound with a target nucleic acid as required by the rejected claims. And there would be no motivation to combine the nucleic acids of the Boom, Matsui, Hayatsu, Holmberg and/or Kariko articles and sell them already bound with a binding agent since the teachings of each of these references is that a solid support, such as a binding-agent, can used to bind a nucleic acid molecule of interest which would otherwise be unbound in solution and where it is desired that such a soluble molecule be bound, and thus captured, on a solid support. That is not the teaching of Applicants' invention where the target nucleic acid is already bound with a binding-agent and the binding-agent is not being used to capture or bind with a nucleic acid that is in solution for purposes of purifying the nucleic acid, and the like. Thus, citing a kit that may perhaps comprise a "binding agent" as defined by Applicants (*e.g.*, specification at page 18, line 9, to page 19, line 20), such as, for instance, a polyamine, siliceous compound, polystyrene, chitin, chitosan, and the like, cannot render obvious Applicants' kit where the target nucleic acid is already bound with the binding agent to form the reference standard in the kit. This argument applies with equal force to the combination of any of the references with the Stratagene kit as asserted by the Examiner in rejection of the kit claims under examination and is therefore not repeated herein for the sake of brevity.

Further, because the combination of the references does not teach or suggest all the claim limitation, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

Therefore, Boom, in view of the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. § 103(a) should be reconsidered and withdrawn.

Rejection of claim 27 pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claim 27 under 35 U.S.C. §103(a) as being *prima facie* obvious over Boom et al. in view of Stratagene Catalog and Holmberg. Specifically, the Examiner is of the opinion that Boom teaches isolated nucleic acid bound to polystyrene particles, and Holmberg teaches binding of oligonucleotides to polystyrene solid support derivatized with an amino group. Therefore, the Examiner reasons that it would have been

prima facie obvious for one skilled in the art to combine the teachings of these references to arrive at the present invention as recited in claim 27. Applicants respectfully submit that the combination of these references do not render the invention *prima facie* obvious for the following reasons.

As discussed elsewhere herein, the teachings of Holmberg and the Stratagene do not correct the deficiencies of Boom such that the combination of these references do not teach the reference standard of Applicants' invention as recited in the claims following entry of the present Amendment. Indeed, the Stratagene kit cannot render these claims obvious as more fully set forth previously elsewhere herein. Nowhere is there teachings of Applicants' reference standard in Holmberg and the Stratagene catalog. Thus, the combination of Boom with Holmberg and the catalog does not teach or suggest all the claim limitations and cannot render the claims *prima facie* obvious. Further, because the combination of the references does not teach or suggest all the claim limitation, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention. Therefore, Boom, in view of Holmberg and the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. § 103(a) should be reconsidered and withdrawn.

Rejection of claim 29 pursuant to 35 U.S.C. § 103(a)

The Examiner has rejected claim 29 under 35 U.S.C. §103(a) as being *prima facie* obvious over Boom et al. in view of Stratagene Catalog and Matsui et al. Specifically, the Examiner is of the opinion that Boom teaches isolated nucleic acid bound to polystyrene particles, and Matsui teaches adsorption (binding) of nucleic acids to low alumina zeolites. Therefore, the Examiner reasons that it would have been *prima facie* obvious for one skilled in the art to combine the teachings of the reference to arrive at the present invention as recited in claim 29. Applicants respectfully submit that the combination of the references do not render the invention *prima facie* obvious for the following reasons.

As discussed elsewhere herein, the teachings of Matsui and the Stratagene do not correct the deficiencies of Boom such that the combination of these references do not teach the reference standard, especially as recited in the claims reciting kits rejected herein. That is, nowhere is there teachings of Applicants' reference standard in Matsui and the Stratagene

catalog. Thus, the combination of Boom with Matsui and the Stratagene catalog does not teach or suggest all the claim limitations and cannot render the claims *prima facie* obvious. Further, because the combination of the references does not teach or suggest all the claim limitation, there would have been no motivation to combine these references, nor any expectation of success that doing so would arrive at the present invention.

Therefore, Boom, in view of Matsui and the Stratagene catalog, cannot render the claims *prima facie* obvious and this rejection under 35 U.S.C. § 103(a) should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each objection and rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1, 3-10, 23, 24, 26-32, is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,

CLARK RUNDELL *ET AL.*

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Date

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